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Review Article

Evolving concepts in the management of antithrombotic therapy in patients undergoing transcatheter aortic valve implantation

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ABSTRACT

Thromboembolic and bleeding complications negatively impact recovery and survival after transcatheter aortic valve implantation (TAVI). Particularly, there is a considerable risk of ischaemic stroke and vascular access related bleeding, as well as spontaneous gastro-intestinal bleeding. Therefore, benefit and harm of antithrombotic therapy should be carefully balanced. This review summarizes current evidence on peri- and post-procedural antithrombotic treatment. Indeed, in recent years, the management of antithrombotic therapy after TAVI has evolved from intensive, expert opinion-based strategies, towards a deescalated, evidence-based approach. Besides per procedural administration of unfractionated heparin, this encompasses single antiplatelet therapy in patients without a concomitant indication for oral anticoagulation (OAC); and OAC monotherapy in patients with such indication, mainly being atrial fibrillation. Combination therapy should generally be avoided to reduce bleeding risk, except after recent coronary stenting where a period of dual antiplatelet therapy (aspirin plus P2Y12-inhibitor) or P2Y12-inhibitor plus OAC (in patients with an independent indication for OAC) is recommended to prevent stent thrombosis. This new paradigm in which reduced antithrombotic intensity leads to improved patient safety, without a loss of efficacy, may be particularly suitable for elderly and fragile patients. Whether this holds in upcoming populations of younger and lower-risk patients and in specific populations as patients with subclinical valve thrombosis, is yet to be proven. Finally, whether less intensive or alternative approaches should be also applied for the periprocedural management of the antithrombotic therapy, has to be determined by ongoing and future studies.

1. Introduction

Transcatheter aortic valve implantation (TAVI) is an effective and less invasive treatment option compared with conventional surgical aortic valve replacement (SAVR), and is the standard of care for patients with severe aortic stenosis considered inoperable or at high surgical risk [1,2]. Currently, the indication for TAVI is shifting towards younger and lower risk patients [3–6]. Although TAVI techniques and the risk level of the treated population have improved over time, thromboembolic and bleeding complications are still frequent and negatively impact recovery and survival after TAVI.[7] To prevent thromboembolic, in particular cerebrovascular events, antithrombotic therapy is recommended in all TAVI patients.[1,2] However, recent evidence underlines to be cautious with intensive antithrombotic treatment, given the associated risk of bleeding in the current TAVI population [8–10]. This poses a challenge on clinical practise, especially in the elderly TAVI population, to strike the optimal balance between thromboembolic and bleeding risk. Therefore, in this review we provide an overview of the most recent evidence regarding the optimal antithrombotic therapy in patients undergoing TAVI.

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2. Thromboembolic risk and bleeding risk

The incidence of thromboembolic events varies between 3 and 15% within the first year following TAVI, depending on the risk level of the treated population [3–16]. This involves the occurrence of ischaemic stroke and transient ischaemic attack (~1–7%), myocardial infarction (~0.5-2%), systemic thromboembolism (~0.5–2%), intra-cardiac thrombus (0.5–1%) and obstructive valve thrombosis (~0.5-3%) [3–14]. These complications have devastating effects, especially ischaemic stroke, leading to permanent disability or death in many of the affected patients [7,11]. Most of the thromboembolic events occur within the first 48 hours, followed by an ongoing increased incidence in the first months with a gradual decrease thereafter [3–6,11–14,16]. The underlying pathophysiological mechanism is assumed to be multifactorial and is related to both patient- and procedure-related characteristics. Procedural factors explain most of the events in the acute periprocedural phase, caused by the interaction between the device and the calcified aortic valve, with debris dislodgment due to the placement of wires and catheters, valve deployment and pre- and post-dilatation [17]. Histopathologic studies on periprocedural emboli demonstrated that embolization occurs in the majority of patients, including thrombus, calcium, tissue fragments, and foreign material [18,19]. New-onset atrial fibrillation (NOAF) explains part of the thromboembolic events during the early postprocedural phase [11,20]. A meta-analysis (n=14,078; 26 trials) regarding this issue reported an incidence of 17.5% NOAF after TAVI. Although very common, pre-existing atrial fibrillation did not, but NOAF did increase the risk of stroke significantly in the short-term [20]. Furthermore, the early high-risk period might be caused by the lack of endothelialisation of the newly implanted transcatheter valve [21]. The native anatomy of the patient and the deployed TAVI valve together create a unique anatomic geometry, which can lead to stagnant blood flow in the neo-sinus (region between the native and transcatheter aortic valve leaflet) [17,22]. This stagnant flow may allow blood to stay in prolonged contact with the foreign surface of the transcatheter heart valve and result in thrombosis [22]. Finally, thromboembolic risk is also enhanced by coexisting atherosclerotic disease. TAVI patients often suffer from coronary, cerebrovascular and peripheral artery disease, which increase the risk of subsequent thromboembolic events until in the late postprocedural phase [23]. In the elderly, the CHA2DS2-VASc score may help to quantify thromboembolic risk and give an indication of frailty status [24]. Also, specific frailty assessment tools, like the Edmonton Frail Scale, may identify individuals at highest risk of a poor outcome [7,24,25].

The incidence of major bleeding varies between 3 and 17% in the first year after TAVI and consists of periprocedural (mainly vascular access related) bleeding and spontaneous bleeding [3–10,12–14,26,27]. Most spontaneous bleeding events occur in the gastro-intestinal or urogenital tract [9,10]. Vascular access related bleeding has decreased over time, due to routine contrast-enhanced CT assessment of vascular anatomy, ultrasound-guided vascular puncture, smaller bore catheters and the use of better closure devices. Still, vascular access related bleeding accounts for half of all major bleeding events. Non-transfemoral access and sheath diameter have been reported as procedural risk factors [28]. Patient related risk factors include higher age, frailty and frequent comorbidities like renal insufficiency, anaemia and atrial fibrillation [28–32]. Furthermore, aortic stenosis related conditions like acquired type 2A von Willebrand factor (vWF) defect, angiodysplasia, (transient) trombocytopenia and Heyde's syndrome increase the hazards of bleeding [33,34]. This complex bleeding diathesis is further amplified by the use of antithrombotic drugs, especially in elderly patients who are frequently affected by multimorbidity and subsequent polypharmacy which expose them to potential pharmacological interactions [35].

3. Periprocedural antithrombotic therapy

Before TAVI, a loading dose of aspirin is usually administered to patients without a pre-existent indication for antiplatelet therapy [36]. In patients already on antiplatelet therapy this is often continued during TAVI as single antiplatelet therapy (SAPT), except for patients with recent coronary stenting in whom dual antiplatelet therapy (DAPT) is indicated [36,37]. Several studies have shown that adding clopidogrel before TAVI, either using a loading dose or as maintenance therapy, is not associated with any patient benefit [10,38,39]. However, the optimal timing of administration (before or after TAVI) and type of SAPT (Aspirin or a P_2Y_{12} inhibitor) still lacks of supporting evidence.

Periprocedural practice differs widely in patients with OAC (e.g. for atrial fibrillation). Studies report perioperative interruption of OAC 2-7 days prior to TAVI, as well as full continuation of OAC [40–45]. Also, some clinics use unfractionated heparin, low molecular weight heparin or aspirin for bridging in patients in whom OAC is interrupted, whereas others do not [40–45]. Interestingly, a recent observational study (n = 1317) reported that continuation of OAC was associated with a similar rate of major or life-threatening bleeding and major vascular complications compared with interruption. Stroke rates were numerically higher in patients with interruption of OAC, but this did not reach statistical significance [40]. However, considering the numerous limitations associated with this retrospective analysis [46], these results need robust confirmation before they can inform clinical practice. The results of the 'Periprocedural Continuation Versus Interruption of Oral Anticoagulant Drugs During Transcatheter Aortic Valve Implantation (POPular PAUSE TAVI) trial' (NCT04437303) will provide more evidence on this topic.

Per procedural, parenteral anticoagulation is administered to prevent catheter thrombosis and possibly reduce periprocedural thromboembolism [36]. The BRAVO 3 Trial (n = 802) demonstrated non-inferiority, but not superiority of bivalirudin versus unfractionated heparin in the occurrence of major bleeding and net adverse cardiovascular events (all-cause mortality, myocardial infarction, stroke or major bleeding) within 30 days after TAVI [47]. Because bivalirudin is more expensive and requires continuous infusion, unfractionated heparin remains the first-line drug [48]. Bivalirudin serves as a valuable alternative in the presence of contraindications like heparin-induced thrombocytopenia [36,48]. Furthermore, unfractionated heparin can be reversed using protamine sulphate in order to reduce bleeding complications. This has been adopted from its use in cardiac surgery and is supported by low-level evidence [49–51]. One retrospective study (n=873) reported that heparin reversal by protamine administration resulted in significantly lower rates of life-threatening and major bleeding complications compared with patients without heparin reversal. No signs of a prothrombotic effect were observed [49]. More recent, the PS TAVI trial, a small single-centre randomized clinical trial (n=100) reported a non-significant but substantial reduction in major or life-threatening bleeding with protamine versus placebo [50]. The numerous limitations of both studies warrant larger trials, since protamine can cause allergic reactions including anaphylaxis, hypotension, bronchospasm and skin reactions in 1-10% of patients [52]. Moreover, at higher doses, protamine may have significant anticoagulant and antiplatelet side effects [53]. The results of the 'Effect of routine versus selective protamine administration on bleeding in patients undergoing transcatheter aortic valve implantation' trial (ACTRN12621001261808) will provide more evidence on this topic.

4. Postprocedural antithrombotic therapy

4.1. *In the absence of an indication for oral anticoagulation*

After TAVI, lifelong SAPT is recommended in patients with no indication for OAC (Fig. 1) [2]. This is distilled from several large randomized trials which investigated different antithrombotic strategies

Fig. 1. Preferred antithrombotic regimen according to the clinical setting
VKA= vitamin-K antagonist, NOAC= non-vitamin-K antagonist oral anticoagulants, OAC=oral anticoagulation, PCI=percutaneous coronary intervention.

after TAVI (Table 1). In the GALILEO trial (n=1644), patients were randomized after TAVI to low-dose rivaroxaban plus aspirin for three months, followed by rivaroxaban alone; versus aspirin plus clopidogrel for 3 months, followed by aspirin alone. The trial was prematurely terminated, because the rivaroxaban-based strategy was associated with a higher risk of death or thromboembolic events and a higher risk of bleeding than the antiplatelet-based strategy [8]. Notably, a significant reduction in subclinical leaflet thrombosis was observed in the rivaroxaban group [54]. In stratum 2 of the ATLANTIS trial (n = 1049), patients were randomized after TAVI to full-dose apixaban monotherapy versus standard care antiplatelet therapy (majority DAPT) [55]. Apixaban monotherapy was not superior to antiplatelet therapy in terms of net clinical benefit (mortality, thromboembolic and bleeding events) [56]. Although subclinical leaflet thrombosis was lower with apixaban compared with antiplatelet therapy, this did not lead to an improvement in clinical outcomes [56,57]. In fact, in line with the results of GALILEO (8), more non-cardiovascular deaths occurred in the apixaban group as compared to the antiplatelet group [51]. In contrary to GALILEO and ATLANTIS, cohort A of the POPular TAVI trial (n=690) investigated a deescalated antithrombotic strategy and randomized patients to aspirin monotherapy versus three months of aspirin plus clopidogrel, followed by aspirin alone [10,58]. Significantly lower rates of bleeding were observed in the aspirin alone group without an increase in thromboembolic events [10]. Meta-analyses have substantiated this finding [59–61]. Based on these studies (Table 1), clinical practice has shifted from DAPT in the first 3–6 months after TAVI to lifelong SAPT in patients without coexisting conditions necessitating OAC or DAPT [2,36].

4.2. *In the presence of an indication for oral anticoagulation*

In patients with an indication for OAC, OAC monotherapy is recommended after TAVI (Fig. 1) [2,36]. This is supported by the results of cohort B of the POPular TAVI trial (n=326), which randomized patients with a long-term indication for OAC to OAC alone versus OAC plus three months clopidogrel, followed by OAC alone (Table 1) [9,58]. In line with the results of cohort A, significantly lower rates of bleeding were observed in the OAC alone group without an increase in thromboembolic events [9]. Whether vitamin-K antagonist (VKA) or non-vitamin-K antagonist oral anticoagulants (NOAC) are preferred after TAVI is still unclear. Observational studies are contradictory on this topic [62–64]. In stratum 1 of the ATLANTIS trial (n=451), patients with an indication for OAC were randomized to apixaban versus VKA [55,56]. Similar rates of mortality, thromboembolic and bleeding events were observed between the study groups, consequently the trial failed its primary hypothesis of superiority of apixaban over VKA [56]. However, since the number of OAC patients was too small to provide sufficient evidence for this hypothesis, definitive conclusions on the safety and efficacy of apixaban as compared to VKA cannot be drawn from this trial. The ENVISAGE-TAVI AF trial (n = 1426), randomized patients to edoxaban versus VKA [65,66]. Similar rates of the primary composite outcome including mortality, thromboembolic and major bleeding events occurred between the trial arms and non-inferiority of edoxaban as compared to VKA was proven. Nevertheless, major bleeding was significantly higher in the edoxaban group, mainly due to an increase in gastro-intestinal bleeding [66]. This was not observed in patients who

Table 1
Overview of randomized clinical trials investigating the effect of different antithrombotic strategies after TAVI on clinical endpoints.

Study	Year	N	Comparison	Main endpoints	Main results
Randomized clinical trials including patients without an indication for oral anticoagulation:					
Ussia et al. [86]	2011	79	SAPT (aspirin) vs. 3 months DAPT (aspirin + clopidogrel) followed by SAPT	Composite of all-cause mortality, MI, major stroke, or life-threatening bleeding or urgent conversion to surgery at 6 months.	No significant difference in the primary composite endpoint (15% vs 18% respectively, p=0.85)
SAT-TAVI [87]	2014	120	SAPT (aspirin) vs. 6 months DAPT (aspirin + clopidogrel or ticlopidine)	All-cause mortality, major vascular complications, life-threatening or disabling bleeding, acute kidney injury stage 3, major stroke, MI, repeat procedure or valve related dysfunction according to VARC-2 at 30 days.	No significant differences in VARC-2 endpoints, except more vascular complications in the DAPT compared to SAPT group (13.3% vs 5%, p<0.05)
ARTE [88]	2017	222	SAPT (aspirin) vs. 3 months DAPT (aspirin + clopidogrel)	Primary composite of all-cause mortality, MI, stroke or TIA, or major or life-threatening bleeding according to VARC-2 at 3 months.	The primary composite endpoint was numerically higher in the DAPT group (15.3% vs. 7.2%, p=0.065). DAPT was associated with a higher rate of major or life-threatening bleeding (10.8% vs. 3.6%; p=0.038). There were no differences in the occurrence of death, MI, stroke or TIA.
GALILEO [8]	2020	1644	3 months rivaroxaban 10mg + SAPT (aspirin) followed by rivaroxaban 10 mg vs. 3 months DAPT (aspirin + clopidogrel) followed by SAPT	Composite of all-cause death or thromboembolic events and the composite of life-threatening, disabling or major bleeding according to VARC-2 after a median of 17 months	Higher rate of all-cause death or thromboembolic events (9.8 vs. 7.2 per 100 person-years, HR 1.35. p=0.04) and bleeding (4.3 vs. 2.8 per 100 person-years, HR 1.5, p=0.08) in the rivaroxaban group.
POPular TAVI [10] (cohort A)	2020	665	SAPT (aspirin) vs. 3 months DAPT (aspirin + clopidogrel) followed by SAPT	All bleeding, non–procedure-related bleeding, the composite of cardiovascular mortality, non-procedural bleeding, stroke, or MI and the composite of cardiovascular mortality, ischaemic stroke, or MI at one year.	Lower risk of all bleeding (15.1% vs. 26.6%, RR 0.57, p=0.001), non–procedure-related bleeding (15.1% vs 24.9%, RR 0.61, P=0.005), and the composite of cardiovascular mortality, non-procedural bleeding, stroke, or MI (23.0% vs. 31.1%, RD -8.2, p=0.04) in the SAPT group. No difference in the composite of cardiovascular mortality, ischaemic stroke, or MI.
ATLANTIS [56] (stratum 2)	2021	1049	Apixaban monotherapy vs. standard of care antiplatelet therapy (majority DAPT)	Efficacy outcome: death, MI, stroke, intracardiac or valve thrombosis, systemic emboli, deep vein thrombosis or pulmonary embolism. Safety outcome: life-threatening, disabling or major VARC-2 bleeding at one year.	No significant difference in the efficacy outcome (16.9% vs. 19.3%, HR 0.88, 95% CI 0.66-1.17) and the safety outcome (7.8% vs. 7.3%, HR 1.09, 95% CI 0.69-1.69) between the study groups. Higher risk of non-cardiovascular mortality (2.66% vs. 0.96%) in the apixaban group.
Randomized clinical trials including patients with an indication for oral anticoagulation:					
POPular TAVI [9] (cohort B)	2020	313	OAC monotherapy vs. OAC + 3 months SAPT (clopidogrel) followed by OAC alone	All bleeding, non–procedure-related bleeding, the composite of cardiovascular mortality, non-procedural bleeding, stroke, or MI and the composite of cardiovascular mortality, ischaemic stroke, or MI at one year.	Lower risk of all bleeding (21.7% vs. 34.6%, RR 0.63, p=0.01), non–procedure-related bleeding (21.7% vs 34.0%, RR 0.64, P=0.02), and the composite of cardiovascular mortality, non-procedural bleeding, stroke, or MI (31.2% vs. 45.5%, RR 0.69, 95% CI for superiority 0.51 to 0.92) in the OAC monotherapy group. No difference in the composite of cardiovascular mortality, ischaemic stroke, or MI.
ATLANTIS [56] (stratum 1)	2021	451	Apixaban vs VKA	Efficacy outcome: death, MI, stroke, intracardiac or valve thrombosis, systemic emboli, deep vein thrombosis or pulmonary embolism. Safety outcome: life-threatening, disabling or major VARC-2 bleeding at one year.	No significant difference in the efficacy outcome (21.9% vs. 21.9%, HR 1.02, 95% CI 0.68-1.51) and the safety outcome (10.3% vs. 11.4%, HR 0.92, 95% CI 0.52-1.60) between the study groups.
ENVISAGE-TAVI AF [66]	2021	1426	Edoxaban vs VKA	Efficacy outcome: composite of all-cause death, MI, ischaemic stroke, systemic thromboembolism, valve thrombosis, or ISTH major bleeding. Safety outcome: ISTH major bleeding at a median follow-up of 554 vs. 530 days, respectively.	Edoxaban was non-inferior to VKA regarding efficacy outcome (17.3 vs 16.5 per 100 person-years, p=0.01 for non-inferiority). Significantly higher rates of ISTH major bleeding occurred in the edoxaban group (9.7 vs. 7.0 per 100 person-years; hazard ratio, 1.40; 95% CI, 1.03 to 1.91).

CI=Confidence interval, DAPT=Dual antiplatelet therapy, HR=Hazard ratio, ISTH=International Society on Thrombosis and Haemostasis, MI=Myocardial Infarction, RD=Risk difference, RR=Risk ratio, SAPT=Single antiplatelet therapy, TIA=Transient ischaemic attack, VARC=Valve Academic Research Consortium, VKA=Vitamin K antagonist.

met the dose reduction criteria for edoxaban. So, these criteria should be carefully followed, especially in patients with renal insufficiency. Patients with severe renal insufficiency should be switched to VKA to avoid accumulation and bleeding [30,67]. For clinical practice the results of the ENVISAGE-TAVI AF trial are reassuring with respect to the efficacy of NOACs after TAVI, but do not support proactive postprocedural switching of VKA to NOAC until more evidence on their safety is available.

4.3. After recent coronary stenting

In patients with coronary stenting before or after TAVI, DAPT is recommended in the absence of an indication for OAC to prevent stent thrombosis. The duration of DAPT depends on the indication, being either chronic (CCS) or acute coronary syndrome (ACS), and the bleeding risk of the individual patient. Since TAVI patients are generally at high bleeding risk, as discussed above, the duration of DAPT can be 1-3 months for CCS and 3-6 months for ACS in most cases [36,37]. Accordingly, in patients with an indication for OAC, dual antithrombotic therapy (DAT; i.e. P_2Y_{12} inhibitor plus OAC) is recommended for the same duration [36,37]. Of note, these recommendations are based primarily on studies in patients with coronary artery disease only, because direct evidence in patients undergoing percutaneous coronary intervention before or after TAVI is scarce.

4.4. In patients with (subclinical) valve thrombosis

The incidence of obstructive valve thrombosis, recently defined as clinically significant valve thrombosis [68], varies between 1-3% after TAVI [15,69]. Remarkably, an incidence of 7.6% has been reported in patients after valve-in-valve TAVI, which represents an important risk factor [70]. Obstructive valve thrombosis may lead to symptoms of heart failure or presents as a source of thromboembolism [71]. Therefore, treatment with OAC using a VKA and/or unfractionated heparin is recommended [2].

Subclinical valve thrombosis is more frequent and has been reported in up to 32% of the patients undergoing computed tomography (CT) early after TAVI [54,57,71–74]. This predominantly involves the leaflet (s) of the bioprosthetic valve, without apparent clinical symptoms and is often referred to as subclinical leaflet thrombosis (SCLT) [71]. SCLT seems associated with an increased rate of thromboembolic events, however this association is inconsistent and possibly biased [54,57, 71–82]. Due to the dynamic nature of SCLT - it can occur early or later after TAVI and may resolve spontaneously - it is hard to establish a true causal relationship with the occurrence of thromboembolic events [73]. Furthermore, SCLT may also affect valve durability based on thrombus calcification leading to bioprosthetic valve degeneration [83–85]. However, this link is largely unexplored and even more challenging to investigate. Given the limited evidence of clinically relevant consequences, there is currently no consensus that routine four-dimensional CT screening should be used for diagnosis of SCLT. Although OAC has been proven more effective than antiplatelet therapy in the prevention and treatment of SCLT (see also section *Postprocedural Antithrombotic Therapy - In the absence of an indication for oral anticoagulation*), it is uncertain whether this also translates into improved clinical outcomes. Taking into account the associated risks of OAC exposure in the current frail TAVI population, this warrants further investigation. Meanwhile, recent ESC guidelines state that anticoagulation should be considered in patients with leaflet thickening and reduced leaflet motion leading to elevated gradients, at least until resolution [2].

5. Conclusions

The management of antithrombotic therapy after TAVI has evolved from rather intensive, expert opinion-based strategies, towards a deescalated, evidence-based approach. This new paradigm in which reduced antithrombotic intensity leads to improved patient safety, without a loss of efficacy, may be particularly suitable for elderly and fragile patients. Whether this holds in upcoming populations of younger and lower-risk patients and in specific populations as patients with subclinical valve thrombosis, is yet to be proven. Finally, whether a less intensive or alternative approaches should be also applied for the periprocedural management of the antithrombotic therapy, has to be determined by ongoing and future studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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